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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,235	07/18/2000	Donn Nelson Rubingh	7670	8554

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THE PROCTER & GAMBLE COMPANY
PATENT DIVISION
SHARON WOODS TECHNICAL CENTER
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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1652

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DATE MAILED: 01/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/618,235

Applicant(s)

RUBINGH ET AL.

Examiner

William W. Moore

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-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 November 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2-5 & 7. 6) ☐ Other: _____

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DETAILED ACTION*Information Disclosure Statement*

The information disclosure statement filed December 4, 200, fails, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because three publications cited therein, numbered 43, 52 and 53, lack publication dates, a necessary element for consideration. While the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not. Applicant is advised that the date of any re-submission of these citations contained in this information disclosure statement or the submission of the missing element – their publication dates – will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Election/Restrictions

Applicant's election with traverse in Paper No. 9 filed November 2, 2001, of any of six species of protease having an epitope-masking conjugate is acknowledged. Because the election of Paper No. 9 was incomplete – naming six species of substituted and conjugated proteases rather than one as required in Paper No. 8 mailed October 2, 2001 – a telephonic election of a further, single, species among the six was requested of Applicant's counsel on January 8, 2002. The traversal is on the grounds that there would be no undue burden in joint examination because the positions for substitution and conjugation are not enumerable and are closely related. This is not found persuasive because the positions for conjugation instead number nearly fifty if only the single substitutions and conjugations are considered, because Applicant declines to explain the nature of the close relationship among any set of the positions, and because Applicant does not allege that any of the substituted and conjugated protease species, i.e., any single, double, or multiple set

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of substitutions and conjugations, might be patentably indistinct, one from another, nor submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case.

During a telephone conversation with Ms. Dara M. Kendall on January 8, 2002, a further provisional election was made **with** traverse to prosecute the invention of protease conjugate having protection of an epitope region due to a substitution and conjugation at position 17 in a first epitope region, position 52 in a second epitope region, and position 155 in a third epitope region, represented in claims 1-21. Applicant in replying to this Office action must make affirmation of this election. Applicant indicates that examination is desired of proteases modified with an epitope-masking conjugation at each of positions 17, 52, 89, 134, 155 and 265, and single substitutions and accompanying epitope-masking conjugations at these positions are considered a reasonable number of species for examination. The requirement, as modified by Applicant's request, is still deemed proper and is therefore made FINAL. Claims 1-21 are examined to the extent that they describe a protease variant modified by substitution and conjugation at a position that corresponds to any one positions 17, 52, 89, 134, 155 and 265 of the mature subtilisin BPN'.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR §1.48(b) and by the fee required under 37 CFR §1.17(h).

Claims 1-21 raise no issues of enablement or written description under the first paragraph of 35 U.S.C. §112 because the amino acids at each of the subtilisin BPN'-correspondent positions recited in claim 1 may be substituted, if necessary, with a cysteine and then linked according to the teachings of the specification to a polymer or other addition moiety that will mask an epitope at the site of addition. It is not necessary that Applicant exemplify an addition of a masking moiety, whether polymer or polypeptide, at

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each and every position recited in claims 1 and 12 where the procedures and Examples 1-5 at pages 13-18 of the specification demonstrate that Applicant's processes for conjugating addition moieties according to the Group A elected for examination are generally applicable in proteases. Neither does Applicant need to prepare every protease having a clip-site protecting addition moiety at each position stated in claim 1 to meet the statutory requirement for an adequate written description of the elected subject matter. This is because specific identification of positions for addition in the claim corresponding to positions in the amino acid sequence of subtilisin BPN' is considered to reasonably convey to one skilled in the relevant art that Applicant, at the time the application was filed, had constructive possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it does not recite the sequence identifier for the amino acid sequence of subtilisin BPN', set forth in the sequence disclosure as SEQ ID NO:1, thus fails to particularly point out and distinctly claim Applicant's intended subject matter where it does not place a recited position for covalent attachment in the context of a certain amino acid sequence. Claims 2-21 are also subject to this aspect of the rejection because they fail to clarify this ambiguity of the claim from which they depend. Amending each clause of claim 1 to close with the recitation, "positions selected from the group of positions corresponding to positions consisting of . . . of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1", will overcome this aspect of the rejection. Claims 1, 6, 7 and 12 are also indefinite in reciting, "corresponding to subtilisin BPN'", at the close of their constituent clauses or, in the case of claims 7 and 12, at the end of the

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claim, because no single position can correspond to the entire amino acid sequence of the mature protease. Amending claim 1 as suggested above and deleting the phrase, "corresponding to subtilisin BPN'", from the clauses of claims 1, as well as from claims 6, 7 and 12 wherein it is unnecessary since all depend ultimately from claim 1, will overcome this aspect of the rejection.

Claims 5 and 11 are independently indefinite in reciting, at the end of each claim, "and variants thereof", where the claim construction is that of a Markush claim wherein each element must be defined, and where four of the recited proteases that may be part of a protease conjugate are disclosed in the specification to be specific variants of subtilisin BPN'. Thus the scope of a claim reaching undefined variants of four different defined variants as well as of the native subtilisins cannot be determined.

Claim 19 is independently indefinite in reciting, "additionally comprising one or more supplementary moieties", because one cannot determine neither the part nor aspect of the protease conjugate of claim 1 is to be supplemented or the nature of the supplement. Is it the protease, the addition moiety, or an amino acid or a residue of the protease that Applicant intends supplemented? Applicant must determine what is intended by this claim and provide (a) structural description(s) of, and indicate the nature of, (a) supplementary moiety(ies) so that the public can know what the resulting product might be in order to overcome this aspect of the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the

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5 various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1-6, 8, 9 and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable over von der Osten et al., U.S. Patent No. 6,300,116, and Braxton et al., U.S. Patent No. 5,766,897, both made of record herewith.

10 Von der Osten et al., available as prior art under 35 U.S.C. 102(e) in view of their earlier filing date, teach, see Table 3, that the amino acid at position 132 in subtilisin 309, a position corresponding to the subtilisin BPN' position 134, may be altered by a generic amino acid substitution to inhibit autoproteolysis. Von der Osten et al. further disclose the preparation of detergent cleaning compositions comprising such autoproteolysis-resistant subtilisin variants. Braxton et al., teach the substitution of cysteines for native
15 amino acids in a protein to then conjugate polymers, including polyethylene glycol [PEG] polymers, having structure meeting limitations of the addition moiety described in claims 2, 10, 11, 16 and 17 herein, in order to mask epitopes that may be recognized by a mammalian immune defense system.

20 It would have been obvious for one of ordinary skill in the art to protect proteolysis-susceptible regions of a subtilisin, such as the position corresponding to the subtilisin BPN' position 134 identified by von der Osten et al., by substituting a cysteine for the native amino acid at either of the subtilisin BPN'-correspondent positions 161 and 162 and conjugating a PEG polymer to the cysteine with the procedures taught by Braxton et al.,
25 meeting limitations of claims 1-6, 8 and 9. Such an artisan would have been motivated to use the procedures of Braxton et al. to mask the proteolysis-susceptible region from the autoproteolysis in preparing a subtilisin variant as a component of a detergent composition, substituting a cysteine for an amino acid at the subtilisin BPN'-correspondent position 134 and then conjugating a PEG polymer to the substituting cysteine because the artisan would
30 reasonably have expected that the teachings of Braxton et al. of masking a polypeptide

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region from immune surveillance would advantageously be extended to masking a proteolysis susceptible site with a PEG polymer which would render the region unavailable for attack by the catalytic site of subtilisins. It would further have been obvious to such an artisan to incorporate a subtilisin having a conjugation of a PEG polymer at the subtilisin BPN'-correspondent position 134 in a cleaning composition of claim 20 because the artisan could reasonably expect that a protease conjugate would be more stable than a corresponding unconjugated subtilisin due to its resistance to autoproteolysis.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over von der Osten et al. ('116) and Braxton et al., as applied to claims 1-6, 8, 9 and 20 above, and further in view of Powell et al., U.S. Patent No. 6,060,546, made of record herewith.

The teachings of von der Osten et al. and Braxton et al. discussed above, are taken as before. Powell et al., available as prior art under 35 U.S.C. 102(e) in view of their earlier filing date, teach, see paragraph spanning cols. 16 and 17, the preparation of a personal care composition comprising a subtilisin. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a personal care composition according to Powell et al. and substitute a protease conjugate obvious over the teachings of von der Osten et al. and Braxton et al., for that used by Powell et al. because such an artisan at that time would have had a reasonable expectation that a protease conjugate resistant to autoproteolysis would have at least comparable, if not greater, stability and would advantageously fulfill the same role as well as the subtilisin taught by Powell et al.

Allowable Subject Matter

Protease conjugate species having an addition moiety covalently attached at the subtilisin BPN'-correspondent positions 17, 52, 89, 155 and 265 are free of the prior art made of record with Applicant's Information Disclosure Statements and the prior art made of record herewith. While Estell et al., U.S. Patent No. 6,218,165, made of record herewith, and Løvborg, WO 92/10755, made of record with Applicant's Information Disclosure Statements, both disclose many subtilisin amino acid positions identified by

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correspondence with positions in the sequence of subtilisin BPN', that may be substituted, or conjugated to non-allergenic moieties, e.g., a polyethylene glycol or dextran polymer, in order to reduce the allergenicity of a subtilisin, no position is in a region corresponding to amino acid positions 17, 52, 89, 155 and 265 of subtilisin BPN'. The only prior art discussion of amino acid sequence modifications at a position corresponding to amino acid positions 17 of subtilisin BPN' are those of Branner et al., U.S. Patents Nos. 5,482,849 and 5,631,217, made of record herewith, who disclose a substitution of glutamine for the native histidine present at this position in subtilisins BPN' and 309. Subtilisins Carlsberg and DY have a glutamine at this position, thus one of ordinary skill in the art would have had no expectation that adding an epitope-masking PEG conjugate at this position would reduce antigenicity of a subtilisin. No prior art of record discusses amino acid sequence modifications at a position corresponding to amino acid position 52 of subtilisin BPN' which is a proline in subtilisins BPN' and 309 and an alanine and a serine in, respectively, subtilisins Carlsberg and DY, thus one of ordinary skill in the art would have had no expectation that adding an epitope-masking PEG conjugate at this position would reduce antigenicity of a subtilisin.

Prior art discussions of amino acid sequence modifications at a position corresponding to amino acid positions 89 of subtilisin BPN' include those of van Eekelen et al., U.S. Patent No. 5,324,653, made of record herewith, disclose teach substitutions of glutamine or serine for the glutamate at the subtilisin BPN'-correspondent position, amino acids naturally occurring at this position in other native prior art subtilisins, and Christianson et al., U.S. Patent No. 5,340,735, made of record herewith, who disclose substitutions of arginine or methionine for a glutamate at the subtilisin BPN'-correspondent position. One of ordinary skill in the art would have had no expectation that adding an epitope-masking PEG conjugate at this position would reduce antigenicity of a subtilisin where no prior art

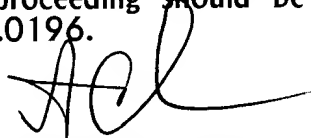
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suggests that the region comprising it contributes to an epitope region. Similarly, while many publications in the prior art discuss amino acid substitutions for the conserved asparagine at the subtilisin BPN'-correspondent position 155, see, e.g., Estell et al. EP O 251,466, made of record with Applicant's Information Disclosure Statement, one of
5 ordinary skill in the art would have had no expectation that adding an epitope-masking PEG conjugate at this position would reduce antigenicity of a subtilisin where no prior art suggests that the region comprising it contributes to an epitope region.

Lysine is the amino acid present at position 265 of the amino acid sequence of subtilisin BPN' and, according to Delgado et al., 1992, a target for PEG conjugation of
10 prior art methods. While subtilisin 309 has been conjugated with PEG in the prior art to reduce its allergenicity, it cannot be said that a subtilisin BPN'-correspondent position 265 in subtilisin 309 might contribute to an epitope whereby allergenicity was reduced by a PEG conjugation because serine, rather than lysine is present at the position in subtilisin 309. Consequently, one of ordinary skill in the art would have had no expectation that
15 adding an epitope-masking PEG conjugate at this position would reduce antigenicity of a subtilisin where no prior art suggests that the region comprising it contributes to an epitope region.

Conclusion

Any inquiry concerning this communication or earlier communications from the
20 examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. The examiner's direct
25 FAX telephone number is 703.746.3169. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or
30 relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.


PONNATHAPU ACHUTAMURTHY
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William W. Moore
January 11, 2002